

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment filed August 18, 2008 has been entered claims 1 and 8 have been amended. Claims 2-3, 9-11 and 22 have been canceled. Claims 1, 4-8, 12-21 and 23-24 are under examination.

2. The Declarations filed under 37 CFR 1.132 filed August 18, 2008 are acknowledged.

The Declarations of Dr. Bruce P. Capehart and Dr. Eric Finzi under 37 CFR 1.132 filed August 18, 2008 are insufficient to overcome the rejection of claims 1-15 and 23 and 24 as set forth in the last Office action.

Rejections Maintained

3. The rejection of claims 1, 4-8, 12-15 and 23-24 under 35 U.S.C. 103(a) is maintained for the reasons set forth on pages 2-7, paragraph 3 of the previous Office Action.

The rejection is reiterated below:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The claims are rejected under 35 U.S.C. 103(a) as unpatentable over Jahanshahi et al (*Journal of Neurology, Neurosurgery and Psychiatry* (1992, 55:229-231) in view of Binder (*U.S. Patent No. 5,714, 468 published February 3, 1998*) and further in view of Carruthers et al (*U.S. Patent No. 6,358, 917 B1, published March 19, 2002*).

The claims are directed to a method of treating major depression or dysthymia in subject comprising administering to the subject with primary depression a therapeutically effective amount of a neurotoxin to a facial muscle to cause paralysis of the facial muscle, thereby decreasing the ability of the subject to frown and treating major depression in the subject.

Jahanshahi et al teach a method of treating patients suffering from depression (e.g. psychological functioning) before and after administration of botulinum toxin (see the Title and the Abstract). Jahanshahi et al teach that depression can result from primary central neurotransmitter dysfunction (page 229). Jahanshahi et al teach that in this study there was a significant improvement in depression of patients that received botulinum toxin injections (page 231). Jahanshahi et al suggest that use of other concepts or techniques may be help with direct management of psychological aspects, body concept and low self-esteem (page 231). Jahanshahi et al that depression may constitute a reaction to the postural abnormality of the head (page 239).

Jahanshahi et al do not teach administering botulinum toxin to a facial muscle such as a frontalis muscle, an orbicularis oculi muscle, procerus muscle, a corrugator supercilli muscle or depressor anguli oris muscle.

Binder teaches that botulinum toxin can be administered to various muscles in the face and head including the frontalis, orbicularis oculi, procerus muscle, a corrugator supercilli and depressor anguli oris (see columns 6-7 and figure 1). Binder teaches that headaches may be associated with depression (column 1). Binder teaches that botulinum toxin when administered to patients with headaches is effective in reducing pain and symptoms associated with or the onset of headaches in mammals (see the Abstract). Binder teaches that botulinum toxin can be administered in a dose of up to about 1,000 units although individual dosages of about 15-30 units are preferred (columns 5-6). Binder teaches that botulinum toxin injection be effective up to about 3 to 6 months (column 7). Therefore the combination of prior art references teach the claim limitation "...further comprising administering an additional dose of 30-50 unit equivalents of botulinum A to the facial muscle after about two to six months".

Jahanshahi et al and Binder do not teach claim limitation "... affecting the ability of the subject to frown".

Carruthers et al teach that botulinum toxin can be used to cause paralysis to a depressor anguli oris in a patient to alleviate downturn at the corners of a patient's mouth (see the Abstract). Carruthers et al teach that this condition is called "sad mouth" column 2).

It would be *prima facie* obvious at the time the invention was made to administer botulinum toxin to patients suffering from depression as well as affecting the ability of the patient to frown or scowl because Jahanshahi et al teach that administering botulinum toxin to torticollis patients experiencing depression significantly reduced levels of depression and anxiety, Binder teaches that botulinum toxin can be effectively administered to facial muscles such as the frontalis, orbicularis oculi, procerus muscle, a corrugator supercilli and depressor anguli oris and Carruthers et al teach that botulinum toxin can be used to cause paralysis to a depressor anguli oris in a patient to alleviate downturn at the corners of a patient's mouth. Based on the teachings of the combined prior art references, it would be expected barring evidence to the contrary, that the administration of botulinum toxin to the facial muscles of patients suffering from depression would be an effective way to treat depression as well as anxiety in these patients.

Applicant's Arguments

A) Applicant urges that the claimed methods are not obvious over the prior art of record. Applicant urges that according to MPEP 2141 rationales that may support a conclusion of obviousness include combining prior art elements according to known methods to yield predictable results, simple substitution of one known element for another to obtain predictable results, use known technique to a known device (methods or products) in the same way, applying a known technique to a known device (method or product) ready for improvement to yield predictable results, obvious to try choosing from a finite number of identified, predictable solutions with a reasonable expectation of success, known work in one field of endeavor may prompt variations of it for use in either the same field or a different field on based on design incentives or other market

forces if the variations are predictable to one of ordinary skill in the art and some teaching, suggestion or motivation in the prior art would lead one of ordinary skill in the art to combine prior art teachings to arrive at the claimed methods.

Applicant urges that Jahanshahi et al teach treatment of torticollis by injecting the neck. Caruthers et al teach cosmetic use to alleviate downturn of the mouth. Applicant urges that Binder teaches headache treatments. Applicant urges that there is nothing on the record to combine treatment of torticollis with treatment for headache or teaching of how to cosmetically improve the face. Applicant urges that medical treatments used for one of these conditions simply does not prompt variations based on medical treatments used for a completely different condition, with a completely different etiology.

B) Applicant urges that the Declaration of Dr. Capehart filed under 37 CFR 1.132 confirms that Jahanshahi et al does not suggest to a psychiatrist that botulinum toxin should be used to treat depression in the absence of underlying torticollis. Dr. Capehart discloses in his declaration that a physician's understanding of anatomy and physiology would not predict that injections of botulinum toxin into the neck to have the same effect as injection of botulinum toxin into the corrugator supercilli or procerus muscle as the innervation is entirely different. Dr. Capehart's declaration discloses that a physician also would not look to treat headache as taught by Binder.

C) Applicant urges that there is nothing in Jahanshahi et al, Binder et al or Carruthers et al that suggest to one of ordinary skill in the art to select a subject in the DSM-IV or Beck Depression Inventory and or to treat a subject with major depression by botulinum injection into the corrugator supercilli or the procerus muscle.

D) Applicant urges that a Declaration submitted by Dr. Finzi under 37 CFR 1.132 is provided. In the specification, Dr. Finzi compared the effect of injection of botulinum toxin into the different muscles of the face for treating depression. Applicant urges that injection of botulinum toxin into corrugator supercilli or the procerus muscle provides an unexpected superior result for treatment of depression as compared to injection of botulinum toxin into the orbicularis oculi. Dr. Finzi disclose that injection of botulinum toxin into corrugator supercilli or the procerus muscle were effective while injection of botulinum toxin in the orbicularis oculi and the frontalis were not effective in treating depression supports the conclusion that the method provides unexpected superior results for treatment of depression.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed August 18, 2008 have been fully considered but they are not persuasive.

A) The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the instant case, one of ordinary skill would be motivated to use botulinum toxin to administer botulinum toxin to patients suffering from depression as well as affecting the ability of the patient to frown or scowl because Jahanshahi et al teach a method of treating patients suffering from depression (e.g. psychological functioning) before and after administration of botulinum toxin, Binder teaches that botulinum toxin can be effectively administered to facial muscles such as the frontalis, orbicularis oculi, procerus muscle, a corrugator supercilli and depressor anguli oris and Carruthers et al teach that botulinum toxin can be used to cause paralysis to a depressor angulioris in a patient to alleviate downturn at the corners of a patient's mouth.

To address Applicant comments regarding MPEP 2141, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". Based on the rejection as combined above, it would be obvious to apply a known technique to a known product to be used in a known method that is ready for improvement to yield predictable results.

It should be noted that the claimed invention is directed to a method of treating major depression or dysthymia or primary intermittent anxiety in a subject using specific clinical criteria for major depression or dysthymia or primary intermittent anxiety and administering a therapeutically effective amount of neurotoxin to the corrugator supercilli or procerus muscle thereby decreasing the ability of the subject to scowl or appear sad or frown and thereby treating major depression or dysthymia or primary intermittent anxiety in a subject.

Jahanshahi et al teach a method of treating patients suffering from torticollis as well as depression (e.g. psychological functioning) before and after administration of botulinum toxin. These patients were evaluated using The Beck Depression Inventory, (see Jahanshahi et al page 230, 1st column) which meet the claim limitation "...using specific clinical criteria for major depression or dysthymia or primary intermittent anxiety...". It should be noted that the instant specification at page 13 confirms that this inventory should be used when evaluating patients for depression. . Jahanshahi et al teach that in this study there was a significant improvement in depression of patients that received botulinum toxin injections (page 231). *The prior art teaches success in reducing in depression patients by administering botulinum toxin.*

Binder teaches that botulinum toxin can be administered to various muscles in the face and head including the frontalis, orbicularis oculi, procerus muscle, a corrugator supercilli and depressor anguli oris (see columns 6-7 and figure 1). Binder teaches that headaches may be associated with depression (column 1). *The prior art has*

demonstrated success with administering botulinum toxin to the procerus muscle or a corrugator supercilli muscle.

Carruthers et al teach that botulinum toxin can be used to cause paralysis to a depressor anguli oris in a patient to alleviate downturn at the corners of a patient's mouth (see the Abstract). Carruthers et al teach that this condition is called "sad mouth" column 2). *The prior art teaches success when administering botulinum toxin to achieve a predictable outcome, "frowning or appearing sad".*

Therefore, it would be obvious to one of ordinary skill that the combination of prior art references as combined provided a *prima facie* case of obviousness because it is obvious to combination familiar elements (techniques) according to known methods when it does no more than yield predictable results. The combination of prior art references teach the claimed invention absent convincing evidence to the contrary.

B) To address the Declaration of Dr. Capehart filed under 37 CFR 1.132, it should be noted that this declaration is insufficient to overcome the rejection of claims 1-15 and 23 and 24 as set forth in the last Office action. It should be noted that Dr. Capehart makes an assertion in his declaration that Jahanshahi et al does not suggest to a psychiatrist that botulinum toxin should be used to treat depression in the absence of underlying torticollis. It should be noted that the claimed method is directed to treating major depression or dysthymia or primary intermittent anxiety comprising selecting a subject diagnosed with major depression or dysthymia or primary

intermittent anxiety. The claims are not limited to patients that only suffer from major depression or dysthymia or primary intermittent anxiety since open transitional claim language such as "comprising" is recited in the claimed method. See MPEP 2111 for Transitional Language. Thus, the population of patients taught in Jahanshahi et al fall within the scope of the patients used in the claimed method. To address Dr. Capehart's comments regarding physician's understanding of anatomy and physiology would not predict that injections of botulinum toxin into the neck to have the same effect as injection of botulinum toxin into the corrugator supercilli or procerus muscle, it should be noted that the outcome of the method taught by Jahanshahi et al is that there was a significant improvement in depression (page 231, 1st column). Jahanshahi et al teach that reduction of depression and disability were major psychological benefits of the botulinum toxin injections (page 231, 1st column).

C) As stated above, Jahanshahi et al teach that patients were evaluated using The Beck Depression Inventory, (see Jahanshahi et al page 230, 1st column) which meet the claim limitation "...using specific clinical criteria for major depression or dysthymia or primary intermittent anxiety...". It should be noted that the instant specification at page 13 confirms that this inventory should be used when evaluating patients for depression.

D) To address the Declaration of Dr. Finzi filed under 37 CFR 1.132, it should be noted that this declaration is insufficient to overcome the rejection of claims 1, 4-8, 12-

21 and 23-24 as set forth in the last Office action. To address Dr Finzi comments regarding unexpected superior results, the submission of the objective evidence of patentability does not mandate a conclusion of patentability. See *In re Payne*, 606 F.2d. 303, 203 USPQ 245 (CCPA 1979). The combination of prior art references teach injection of botulinum toxin into the corrugator supercilli or the procerus muscle leads to effective results. The prior art has demonstrated success with administering botulinum toxin to the procerus muscle or a corrugator supercilli muscle.

To address the data disclosed in the Declaration of Dr. Finzi, it is unclear as to where or how this data was obtained. This data is not presented in the instant specification. It is unclear as to if this data was obtained using the methods disclosed in the instant specification. Clarification is required.

In view of all of the above, this rejection is maintained.

4. The rejection under 35 U.S.C. 103(a) is maintained for claims 16-21 for the reasons set forth on pages 7-10, paragraph 4 of the Final Office Action. The rejection is reiterated below:

The rejection was on the grounds that the teaching of Jahanshahi et al, Binder and Carruthers et al as applied to claims 1-15, 22 and 23-24 above and further in view of Wagstaff et al (*Drugs* 2002;62(4):655-703)(*Abstract only*).

Jahanshahi et al, Binder and Carruthers et al have been described previously.

Jahanshahi et al, Binder and Carruthers et al do not teach an additional modality of treatment for depression.

Wagstaff et al teach that paroxetine is a selective serotonin reuptake inhibitor (SSRI) with antidepressant and anxiolytic activity (see the Abstract). Wagstaff et al teach that paroxetine is effective at treating depressive disorder (see the Abstract). Wagstaff et al teach that the common adverse effects with using paroxetine include headache (see the Abstract). Wagstaff et al teach that paroxetine is an important first-

line option for treatment of major depressive disorder, obsessive-compulsive disorder, panic disorder, social anxiety disorder, general anxiety disorder and post-traumatic stress disorder (see the Abstract).

It would be *prima facie* obvious at the time the invention was made to use an additional modality of treatment for depression such as administration of SSRIs to patients suffering from depression because Jahanshahi et al suggest that use of other concepts may be helpful with direct management of psychological aspects such as body concept and low self-esteem. One of ordinary skill in the art would be motivated to administer SSRIs to treat patients with torticollis who suffer from depression because Jahanshahi et al has demonstrated that these patients experience psychological aspects such as body concept and low self-esteem even after botulinum toxin treatment. Therefore, one of skill in the art would reasonably conclude that the addition of a SSRI such as paroxetine would be effective at treating these patients since Wagstaff et al teach that paroxetine is effective in treating depressive disorders such as social anxiety disorder and general anxiety disorder. Based on the teachings of the combined prior art references, it would be expected barring evidence to the contrary, that the administration of botulinum toxin and a SSRI to patients suffering from depression would be effective in treating depression.

Applicant's Arguments

Applicant urges that Wagstaff et al teach that paroxetine (a selective serotonin reuptake inhibitor, SSRI) is effective at treating depression, obsessive-compulsive disorder and panic disorder. Applicant urges that Wagstaff et al is silent on treatments of torticollis, headache and cosmetic procedures. Applicant urges that Diller et al teach that SSRI can cause torticollis. Applicant urges that one of skill in the art would not combine Wagstaff et al with Jahanshahi et al.

Examiner's Response to Applicant's Arguments

The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references

themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the instant case, one of ordinary skill would be motivated to use botulinum toxin to administer SSRIs to treat patients who suffer from depression because Jahanshahi et al has demonstrated that these patients experience psychological aspects such as body concept and low self-esteem even after botulinum toxin treatment. Therefore, one of skill in the art would reasonably conclude that the addition of a SSRI such as paroxetine would be effective at treating these patients since Wagstaff et al teach that paroxetine is effective in treating depressive disorders such as social anxiety disorder and general anxiety disorder. Based on the teachings of the combined prior art references, it would be expected barring evidence to the contrary, that the administration of botulinum toxin and a SSRI to patients suffering from depression would be effective in treating depression.

To address Applicant's comment's regarding paroxetine causing torticollis, it should be noted that the patient in this case was being treated with fluoxetine and benztropine and not specifically, paroxetine. The Abstract of Diller et al provided by Applicant does not indicate that paroxetine alone caused the development of torticollis. It may have been a synergistic effect with the combination of drugs administered.

In view of all of the above, this rejection is maintained.

5. No claims allowed.

Conclusion

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vanessa L. Ford whose telephone number is (571) 272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on (571) 272-0856. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Vanessa L. Ford/
Examiner, Art Unit 1645
October 9, 2008

/N. M. Minnifield/
Primary Examiner,
Art Unit 1645